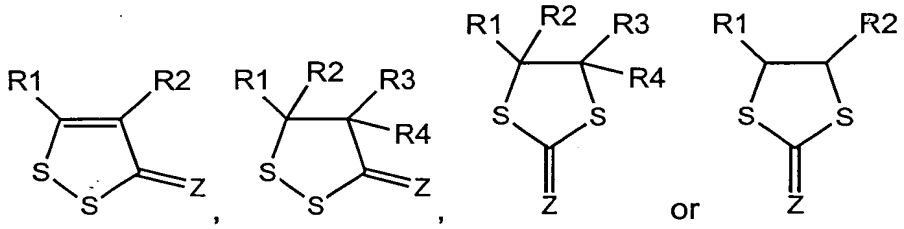
CLAIMS

What is claimed is:

1. A method to treat, prevent or slow the progression of a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, malaria, a leishmania parasite infection or a trypanosome infection, or to ameliorate a symptom thereof, or to treat aluminum intoxication, reperfusion injury, or to reduce the level of iron or to reduce free transition metal ion levels in the body or in certain body compartments, in a subject in need thereof, the method comprising administering to the subject or delivering to the subject's tissues a therapeutically effective amount of a compound having the formula



and oxides, derivatives and metabolites thereof, wherein

Z is S, O, NR, R_2 or CR_2;

R is -H, -OH, C_1-C_5 alkyl, C_1-C_5 alkoxy or C_1-C_5 alkoxycarbonyl;

R_2, together with the atoms to which it is bonded, comprises a spiro or fused ring to yield a bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, -SO_3H, -OH and halogen;

R1, R2, R3 and R4 independently are -H, -alkyl, -aryl, -alkylaryl, a heterocycle, a halogen, -alkoxycarbonyl (C_1-C_5) or -carboxyl,

wherein either alkyl is a C_1-C_{10} linear or branched chain, saturated or unsaturated moiety, which is optionally substituted by 1, 2 or more independently selected ether (-O-), halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), or benzenoid aryl, and

wherein the -aryl and -alkylaryl substituent for R1, R2, R3 and R4 comprises a benzenoid group (C_6-C_{14}), wherein the benzenoid group is optionally substituted with 1, 2 or more independently selected -SO_3H, halogen, alkyl (C_1-C_5), -OH, alkoxy (C_1-C_5), alkoxycarbonyl, (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono- or dialkylamino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), and

wherein the heterocycle is defined as any 4, 5 or 6 membered, optionally substituted heterocyclic ring, saturated or unsaturated, containing 1-3 ring atoms selected from N, O and S, the remaining ring atoms being carbon; and wherein said substituents on said aryl or said heterocyclic are selected from the group consisting of halogen, alkyl (C_1-C_5), hydroxyl, alkoxy (C_1-C_5), alkoxycarbonyl (C_1-C_5), carboxyl, amido, alkyl amido (C_1-C_5), amino, mono and dialkyl amino (C_1-C_5), alkyl carbamoyl (C_1-C_5), thiol, alkylthio (C_1-C_5), benzenoid, aryl, cyano, nitro, haloalkyl (C_1-C_5), alklsulfonyl (C_1-C_5), or sulfonate, or

one of R1 and R2 and one of R3 and R4 together with the carbon atoms to which they are attached comprise a fused bicyclic or tricyclic compound, which is saturated or unsaturated, heterocyclic or carbocyclic and wherein the rings are all optionally substituted 5-, 6-, 7- or 8-membered rings, with substituents optionally selected from alkyl, alkoxy, -SO_3H, -OH and halogen, or

R1 and R2 together or R3 and R4 together independently are oxime (=NOH).

2. The method of claim 1 wherein the compound is selected from the group consisting of oltipraz, 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione, ADT, ADO, 1,2-dithiole-3-thione, 1,2-dithiolane, 1,3-dithiole-2-thione, and malotilate.

3. The method of claim 1 wherein the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction.

4. The method of claim 3 wherein the divalent or trivalent metal ions are selected from Fe, Cu, Ni, Ca, Mg, Mn, Cd, Pb, Al, Hg, Co and Zn ions.

5. The method of claim 4 wherein the divalent or trivalent metal ion is Fe or Cu.

6. The method of claim 1 wherein the degenerative disorder, neurodegenerative disorder, degenerative-related disorder or neurodegenerative-related disorder is selected from the group consisting of Parkinson's disease, Hungtington's disease, Amylotrophic Lateral Sclerosis, Cerebral amyloid angiopathy, Multiple Sclerosis, cognitive disorders, Progeria, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia, HIV-1-associated dementia, post-stroke dementia, Down's syndrome, motor neuron disease, amyloidosis, amyloid associated with type 11 diabetes, Creutzfelt-Jakob disease, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, cerebropathy, neurospanchnic disorders, memory loss and related degenerative disorders.

7. The method of claim 1 wherein the compound is oltipraz and the neurodegenerative disorder is Alzheimer's disease.

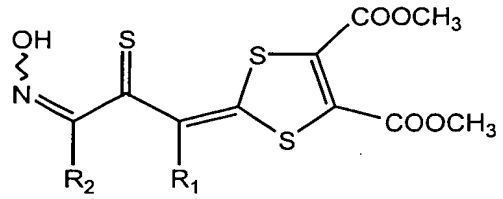
8. The method of claim 1 wherein said compound is a D-amino acid oxidase inhibitor and cellular degeneration is slowed or arrested.

9. The method of claim 1 wherein said compound enhances one or more phase II detoxification enzymes.

10. The method of claim 9 wherein said phase II detoxification is selected from the group consisting of glutathione S transferase, γ-glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase, glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase, and NAD(P)H:quinone oxidoreductase.

11. A method to treat, prevent or slow the progression of a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, malaria, a leishmania parasite infection or a trypanosome infection, or to ameliorate a symptom thereof, or to treat aluminum intoxication, reperfusion injury, or to reduce the level of iron or to reduce free transition metal ion levels in the body or in certain body compartments, in a subject in need thereof, the method comprising administering to the subject or delivering to the subject's

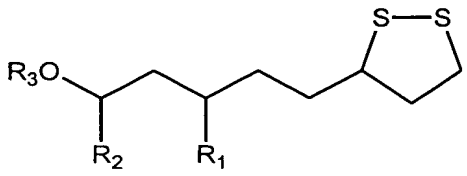
tissues a therapeutically effective amount of a compound having the formula selected from the group consisting of (1), (2), (3) and (4);



(1)

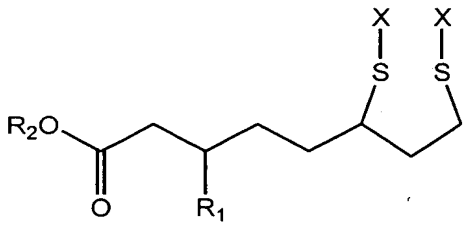
wherein R_1 and R_2 are each independently selected from the group consisting of hydrogen, halogen, nitro, nitroso, thiocyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl, aryl(C_1-C_6 alkyl), aryl(C_2-C_6 alkenyl), carboxyl, (C_1-C_6 alkyl)carbonyl, arylcarbonyl, (C_l-C_6 alkoxy)carbonyl, (C_l-C_6 alkoxy)carbonyl(C_1,-C_6 alkyl), C_1-C_6 alkoxy, trifluoromethyl, amino, di(C_1-C_6 alkyl)amino(C_1-C_6 alkyl), -$NHCOC_nH_{2n+1}$ with n from 0 to 6, -NH—CSC_nH_{2n+1} with n from 0 to 6, terpenyl, cyano, C_2-C_6 alkynyl, C_2-C_6 alkynyl substituted with a C_1-C_6 alkyl or aryl, hydroxy(C_1-C_6 alkyl), a (C_1-C_6 acyl)oxy(C_1-C_6 alkyl), (C_1-C_6 alkyl)thio and arylthio group, or alternatively R_1 and R_2 together form a mono- or poly-cyclic C_2-C_{20} alkylene group optionally comprising one or more hetero atoms and wherein

the aryl group or aryl fraction of said arylalkyl group denotes an aromatic carbon-based group or an aromatic heterocyclic group optionally substituted with one, two or more substituents independently chosen from halogen, C_1-C_4 alky, C_1-C_4 alkoxy group, a trifluoromethyl group, a nitro group and a hydroxyl group;



(2)

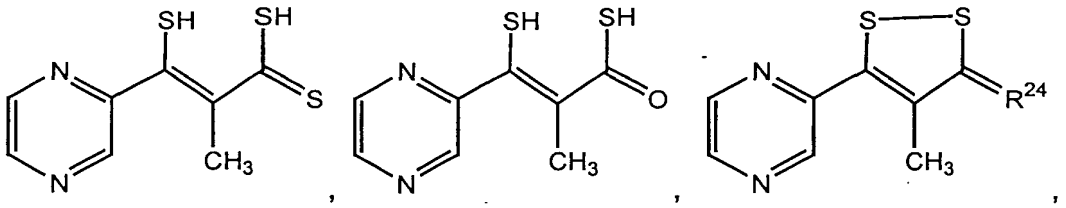
wherein R_1 and R_2 are each independently oxygen (=O) or –OR, where R is H or C_1-C_4 alkyl; and wherein R_3 is H, Na, K or (C_l-C_4) alkyl;

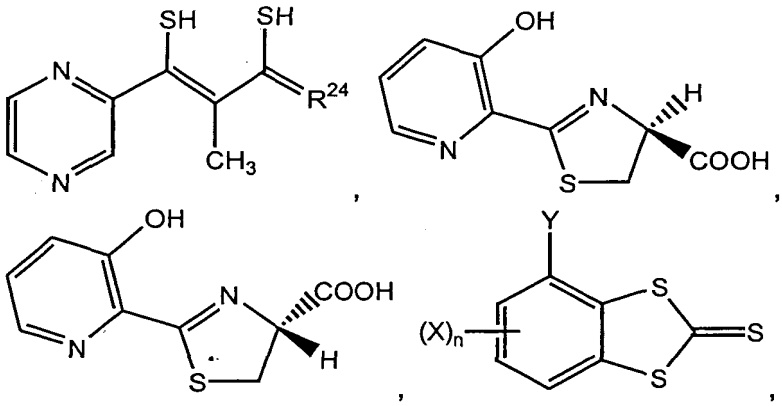


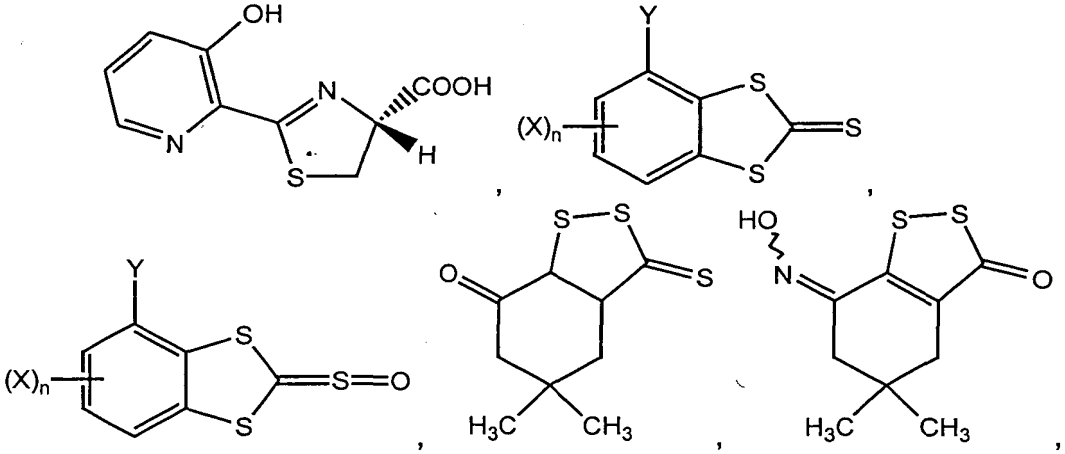
(3)

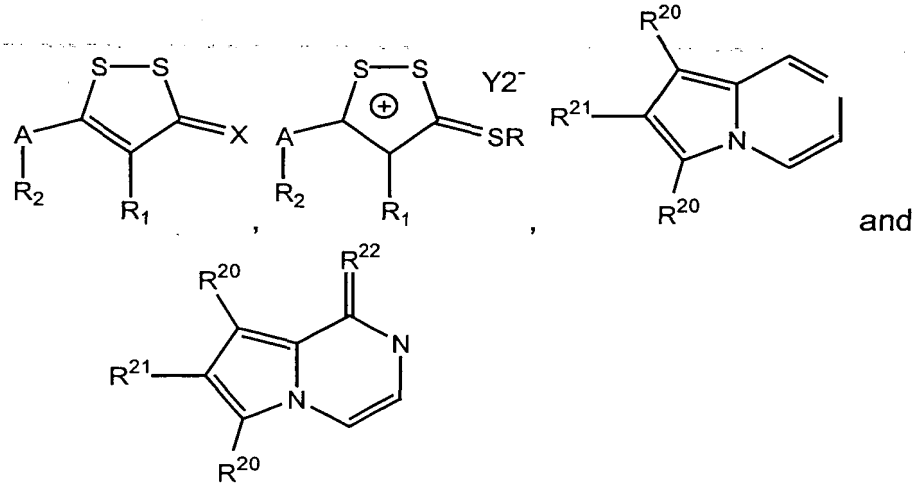
wherein X is H or both Xs represent a direct bond between the two sulfur atoms;

R_1 is =O or -OH; and R_2 is H, Na, K or C_1-C_4 alkyl; and

(4) 







and

wherein

R is C_1-C_6 alkyl;

R_1 and R_2 independently are hydrogen, a halogen, nitro, nitroso, a thiocyano group, a C_1-C_6 alkyl group, a C_2-C_6 alkenyl group, an aryl group, aryl (C_1-C_6 alkyl) group, an aryl (C_2-C_6 alkenyl) group, a carboxyl group, a (C_1-C_6 alkyl) carbonyl group, an aryl carbonyl group, a (C_1-C_6 alkoxy)carbonyl group, a (C_1-C_6 alkoxy)carbonyl (C_1,-C_6 alkyl) group, a C_1-C_6 alkoxy group, a trifluoromethyl group, an amino group, a di(C_1-C_6 alkyl) amino(C_1-C_6 alkyl) group, an acylamino group of formula $-NHCOC_nH_{2n+1}$ with n from 0 to 6, a group $-NH-CSC_nH_{2n+1}$ with n from 0 to 6, a terpenyl group, a cyano group, a C_2-C_6 alkynyl group, a C_2-C_6 alkynyl group substituted with a C_1-C_6, alkyl or an aryl group, a hydroxy(C_1-C_6 alkyl) group, a (C_1-C_6 acyl) oxy (C_1-C_6 alkyl) group, a (C_1-C_6 alkyl) thio group and an arylthio group, or R_1 and R_2 together comprise a mono- or poly-cyclic C_2-C_{20} alkylene group optionally comprising one or more hetero atoms, but they are not 2,2dimethyltrimethylene, or C_3-C_{12} cycloalkylene;

R_3 is hydroxyl, amino, chloro, C_1,-C_4, alkoxy, aryl-C_1,-C_6 alkyl, a (C_1-C_6 alkyl)carbonyl group or R_3 is an aryl (C_1-C_6 alkyl) carbonyl group) or A is -CHOH, >C=O or >C=N-R_4, where R_4 is C_1-C_6 alkyl or aryl group;

R_5, is C_1-C_6 alkyl or aryl;

R^{20} independently is -SH, $-SCH_3$, $-S(O)CH_3$, -OH, $-OCH_3$, -S-C1-C6 alkyl opotionally substituted with 1, 2 or more independently selected -O-, -S-, -OH, halogen, -CN, =O or -C(O)-NH- moieties, or R^{20} independently is -S-C1-C6 alkyl opotionally substituted with 1, 2 or more independently selected -O-, -S-, -OH, halogen, -CN, =O or -C(O)-NH- moieties;

R^{21} is C1-C6 alkyl; and

R^{22} is =O or =S;

R^{24} is =S, =O, =N-OH, =N-R_5, =N-NH-CO-NH_2, =N-NH-CS-NH_2, or =CZZ';

A is oxime or >C=N-OR_3;

n is an integer from 1 to 3;

Y is selected from nitro and trifluoromethyl; X is selected from alkyl and alkenyl of up to 6 carbon atoms, nitro, trichloromethyl, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulfoxyl, trifluoromethylsulfonyl, methoxymethyl, cyano, carboxy, halogen, hydroxy, acetylamino, amino, N-phenylamino, N,N-diallylamino, C_1–C_5 alkoxy, N-morpholino, N-piperidino, N-piperazino, N-pyrrolidino,

dimethylaminodithiocarbarnyl, carboalkoxy, alkylthio, mono- and dialkylamino, N-alkyl-carbamyl, N,N-dialkylcarbamyl, alkylsulfoxy, and alkylsulfonyl, said alkyl groups containing 1, 2, 3 or 4 carbon atoms; and at least one of said X groups is selected from N-morpholino, N-piperidino, N-piperazino or N-pyrrolidino;

Y2 is an acceptable anion; and

Z and Z' independently are -H or an electron-attracting group; and

pharmaceutically acceptable salts thereof.

12. The method of claim 1 wherein the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction.

13. The method of claim 3 wherein the divalent or trivalent metal ions are selected from Fe, Cu, Ni, Ca, Mg, Mn, Cd, Pb, Al, Hg, Co and Zn ions.

14. The method of claim 4 wherein the divalent or trivalent metal ion is Fe or Cu.

15. The method of claim 11 wherein the degenerative disorder, neurodegenerative disorder, degenerative-related disorder or neurodegenerative-related disorder is selected from the group consisting of Parkinson's disease, Hungtington's disease, Amylotrophic Lateral Sclerosis, Cerebral amyloid angiopathy, Multiple Sclerosis, cognitive disorders, Progeria, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia, HIV-1-associated dementia, post-stroke dementia, Down's syndrome, motor neuron disease, amyloidosis, amyloid associated with type 11 diabetes, Creutzfelt-Jakob disease, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, cerebropathy, neurospanchnic disorders, memory loss and related degenerative disorders.

16. The method of claim 1 or claim 11 wherein the compound micronized or the compound is present in a composition that comprises a pharmaceutically acceptable carrier, the carrier optionally selected from phosphatidylcholine, diphosphatidylcholine,

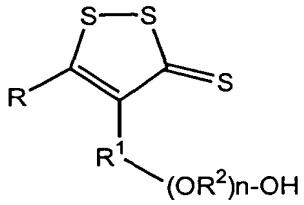
vitamin E, a cyclodextrin, magnolol, a microbial preservative, water or a liquid excipient suitable for ophthalmic pharmaceutical formulations.

17. The method of claim 11 wherein said compound is a D-amino acid oxidase inhibitor and cellular degeneration is slowed or arrested.

18. The method of claim 11 wherein said compound enhances a phase II detoxification enzyme.

19. The method of claim 18 wherein said phase II detoxification enzyme is selected from the group consisting of glutathione S transferase, γ-glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase; glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase and NAD(P)H:quinone oxidoreductase.

20. The method of claim 1, wherein the compound is



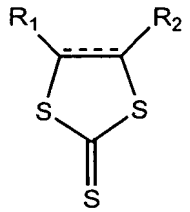
wherein

R is -H or C_1 to C_{12} alkyl;

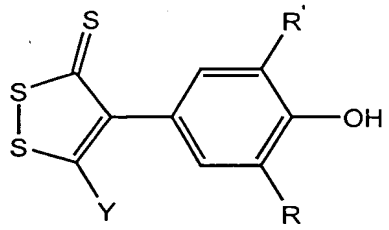
R^1 is C_6 to C_{12} arylene;

R^2 is C_1 to C_4 alkylene; and

n is 2 to 50;



wherein the dotted line is an optional; bouble bond and R_1 and R_2 are independently selected from the group consisting of hydrogen; C_{1-20} alkyl groups and C_{2-12} alkenyl groups;



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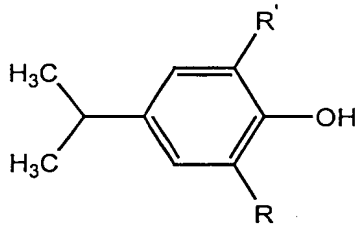


wherein

R and R' independently are C1-C12 alkyl or C3-C12 cycloalkyl, either of which are optionally substituted with C1-C4 alkyl or an aralkyl radical having from 7 to 14 carbon atoms;

Y is -H or -SH; and

R' is C1-C20 alkyl, C5-C12 cycloalkyl, C3-C20 alkenyl, C7-C14 aralkyl.

21. The method of claim 20 which comprises administering or delivering to the subject a therapeutically effective amount of a compound selected from the group consisting of:

4-(3,5-diisopropyl-4-hydroxyphenyl)-1,2-dithiole-3-thione;

4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione;

4-[3,5-bis(l,l-dimethylpropyl)-4-hydroxyphenyl]-1,2-dithi-ole-3-thione;

4-[3,5bis(l,l-dimethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione;

4-[3,5-bis(1,1,3,3-tetramethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione;

4-[3,5-bis(l-methylcyclohexyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione;

4-[3,5-bis(l,l-dimethylbenzyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione;

4-(3t-butyl-4-hydroxy-S-isopropylphenyl)-1,2-dithiole-3-thione;

4-(3t-butyl-4-hydroxy-5-methylphenyl)-1,2-dithiole-3-thione;

4-[3(1,1-dimethylpropyl)-4-hydroxy.-5-isopropylphenyl]-1,2-dithiole-3-thione;

4- [3(1,1-dimethylbenzyl)-4-hydroxy-5-isopropylphenyl]-1,2-dithiole-3-thione;

5-benzylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione;

5-benzylthio-4-[3,5-bis(l,l-dimethylpropyl)-4-hydroxy-phenyl]-1,2-dithiole-3-thione;

5-hexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione; 5-hexylthio-4-[3,5-bis(l,l-dimethylbutyl)-4-hydroxy-phenyl]- 1,2-dithiole-3-thione; 5-octadecylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)- 1,2-dithiole-3-thione; 5-octadecylthio-4-[3,5-bis(l,l-dimethylbenzyl)-4-hydroxyphenyl]- 1,2-dithiole-3-thione; 5-allylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2- dithiole-3-thione; 5--cyclohexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)- 1,2-dithiole-3-thione; and 4-(3,5-di-sec-butyl-4-hydroxyphenyl)-1,2-dithiole -3-thione.

22. The method of claim 20 wherein the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction.

23. The method of claim 22 wherein the divalent or trivalent metal ions are selected from Fe, Cu, Ni, Ca, Mg, Mn, Cd, Pb, Al, Hg, Co and Zn ions.

24. The method of claim 20 wherein the compound is oltipraz and the neurodegenerative disorder is Alzheimer's disease.

25. The method of claim 20 wherein the degenerative disorder, neurodegenerative disorder, degenerative-related disorder or neurodegenerative-related disorder is selected from the group consisting of Parkinson's disease, Hungtington's disease, Amylotrophic Lateral Sclerosis, Cerebral amyloid angiopathy, Multiple Sclerosis, cognitive disorders, Progeria, Alzheimer's disease, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia, HIV-1-associated dementia, post-stroke dementia, Down's syndrome, motor neuron disease, amyloidosis, amyloid associated with type II diabetes, Creutzfelt-Jakob disease, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, cerebropathy, neurospanchnic disorders, memory loss and related degenerative disorders.

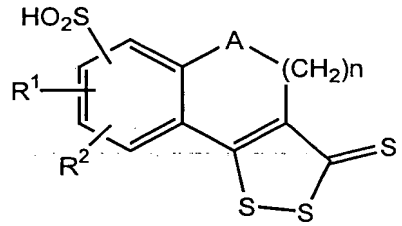
26. The method of claim 20 wherein said compound is formulated into a composition that further comprises a pharmaceutically acceptable carrier.

27. The method of claim 20 wherein said compound is a D-amino acid oxidase inhibitor and cellular degeneration is slowed or arrested.

28. The method of claim 20 wherein said compound enhances a phase II detoxification enzyme.

29. The method of claim 28 wherein said phase II detoxification is selected from the group consisting of glutathione S transferase, γ-glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase; glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase and NAD(P)H:quinone oxidoreductase.

30. A method to treat, prevent or slow the progression of a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, malaria, a leishmania infection or a trypanosome infection, or to ameliorate a symptom thereof, or to treat aluminum intoxication, reperfusion injury, or to reduce the level of iron or to reduce free transition metal ion levels in the body or in certain body compartments, in a subject in need thereof, the method comprising administering to the subject or delivering to the subject's tissues a therapeutically effective amount of a compound having the formula

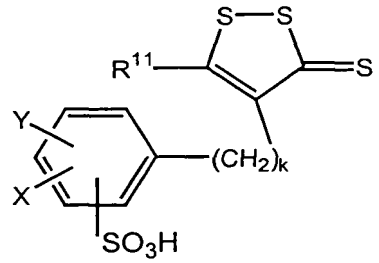


wherein A is a methylene group or an oxygen atom;

R^1 and R^2 are each independently -H, -OH, a halogen, lower alkyl or lower alkoxy; and

n is 0, 1, 2 or 3 when A is a methylene group, and n is 1, 2 or 3 when A is an oxygen atom; or a salt thereof;

or wherein the compound has the formula

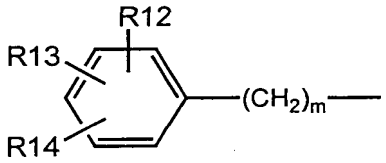


wherein

k is 0, 1, 2, 3, 4 or 5;

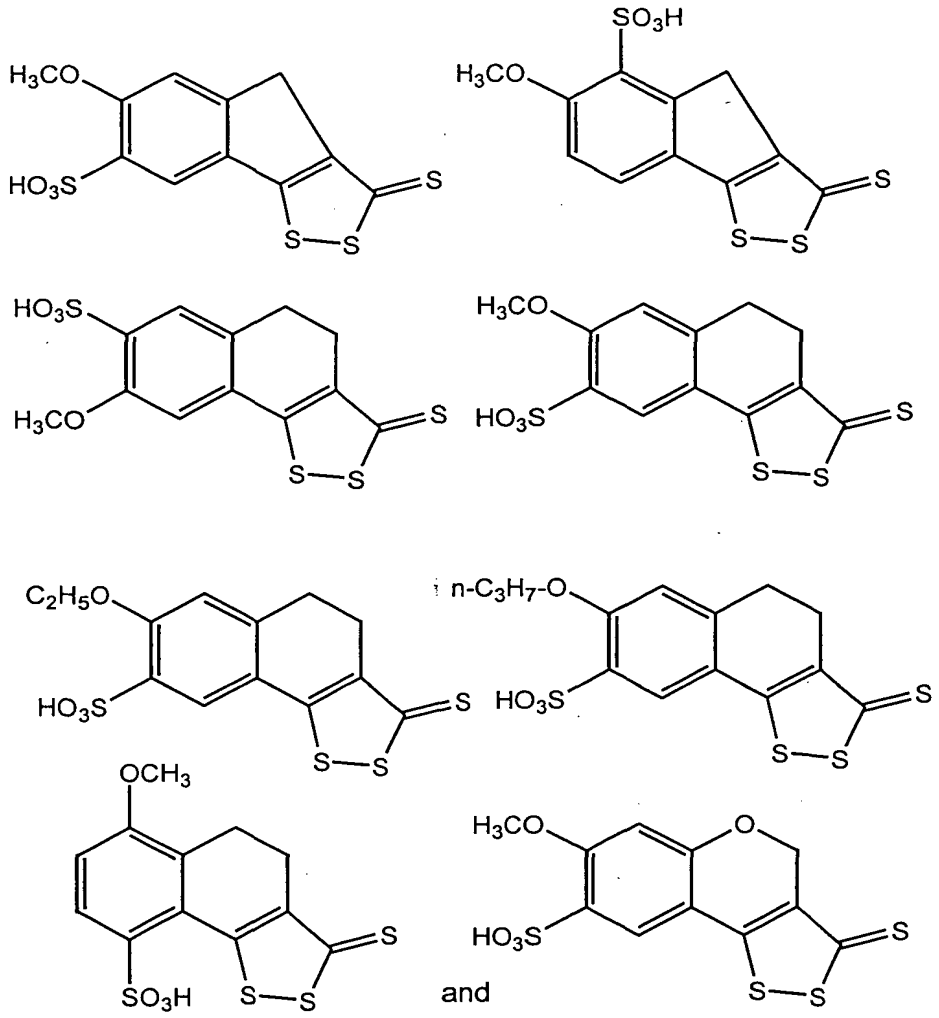
X and Y are independently -H, lower alkyl or lower alkoxy;

R^{11} is an alkyl group or



where m is an integer of 0-4; and R12, R13 and R14 are each independently a hydrogen atom, C_1-C_4 alkyl or C_1-C_4 alkoxy, or a salt thereof, but excluding the compound where k and m are both 0, the sulfo group is bonded to the 3-position, X is 4-methoxy and R12, R13, R14 and Y are all hydrogen.

31. The method of Claim 30 wherein the compound is selected from the group consisting of:



and

32. The method of claim 31 wherein the compound is 5-hexyl-4-(4-methoxy-3-sulfobenzyl)-3H-1,2-dithiole-3-thione, 4-(4-methoxy-3-sulfophenyl)-5-(p-toluyl)-3H-1,2-dithiole-3-thione, or a salt thereof.

33. The method of claim 30 wherein the compound chelates with, or forms a complex with, one or more divalent or trivalent metal ions, whereby the divalent or trivalent ions in the subject's cells or tissues are redistributed or sequestered such that the ions are limited in their capacity to participate in unwanted reactions such as the Fenton reaction.

34. The method of claim 30 wherein the divalent or trivalent metal ions are selected from Fe, Cu, Ni, Ca, Mg, Mn, Cd, Pb, Al, Hg, Co and Zn ions.

35. The method of claim 30 wherein the compound is an oxime or a derivative of said compound.

36. The method of claim 30 wherein said degenerative disorder, *neurodegenerative disorder, degenerative-related disorder or neurodegenerative-related disorder* is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Amylotrophic Lateral Sclerosis, Cerebral amyloid angiopathy, Multiple Sclerosis, cognitive disorders, Progeria, epileptic dementia, presenile dementia, post traumatic dementia, senile dementia, vascular dementia, HIV-1-associated dementia, post-stroke dementia, Down's syndrome, motor neuron disease, amyloidosis, amyloid associated with type II diabetes, Creutzfelt-Jakob disease, necrotic cell death, Gerstmann-Straussler syndrome, kuru and animal scrapie, amyloid associated with long-term hemodialysis, senile cardiac amyloid and Familial Amyloidotic Polyneuropathy, cerebropathy, neurospanchnic disorders, memory loss, aluminum intoxication, reperfusion injury, reducing the level of iron in the cells of living subjects, reducing free transition metal ion levels in mammals, patients having toxic amounts of metal in the body or in certain body compartments, and related degenerative disorders.

37. The method of Claim 30 wherein said compound is formulated into a composition that further comprises a pharmaceutically acceptable carrier.

38. The method of Claim 30 wherein said compound is a D-amino acid oxidase inhibitor.

39. The method of Claim 30 wherein said compound enhances one or more phase II detoxification enzymes.

40. The method of Claim 39 wherein said phase II detoxification is selected from the group consisting of glutathione S transferase, γ-glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase; glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase and NAD(P)H:quinone oxidoreductase.

41. The method of claim 1 wherein the compound comprises at least one adjunct residue that is covalently bonded to the compound, and the adjunct residue is

optionally comprises one to eighty amino acids, which optionally comprise positively charged amino acids.

42. The method of embodiment 41 wherein the positively charged amino acids independently are histidine, arginine or lysine.

43. The method of claim 11 wherein the compound comprises at least one adjunct residue that is covalently bonded to the compound, and the adjunct residue is optionally comprises one to eighty amino acids, which optionally comprise positively charged amino acids.

44. The method of embodiment 43 wherein the positively charged amino acids independently are histidine, arginine or lysine.

45. A method of making oltipraz comprising

esterifying pyrazine-2-carboxylic acid with methanol in the presence of an acid to form methyl-pyrazine-2-carboxylate;

condensing said methyl-pyrazine-2-carboxylate with methyl propionate in the presence of a base to form methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate; and

treating said methyl-2-methyl-3-(pyrazin-2-yl)-3-oxopropionate with phosphorus pentasulfide to form oltipraz.

46. The method of Claim 45 wherein said acid is sulfuric acid and said base is sodium hydride or potassium hydride.

47. The method of Claim 45 wherein said steps (b) and (c) are conducted in the presence of an aromatic hydrocarbon.

48. The method of Claim 47 wherein said aromatic hydrocarbon is toluene.

49. A method to determine if a mammal has a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, or the propensity to develop such a disorder, comprising:

(a) obtaining a circulatory fluid sample from the mammal;

(b) splitting the circulatory fluid sample into two, three or more suitable aliquots;

(c) determining the hydrogen peroxide level in a first aliquot;

(d) contacting a second aliquot with a sufficient amount of a one, two or more D-amino acids;

(e) incubating the second aliquot for sufficient time and under conditions suitable to allow detectable metabolism of the one, two or more D-amino acids to determine the level of hydrogen peroxide in the second aliquot;

(f) determining the hydrogen peroxide level of second first aliquot; and

(g) comparing the hydrogen peroxide level obtained from step (c) and step (f) and the, whereby a high hydrogen peroxide level indicates the presence of a neurodegenerative or related disorder or the propensity to develop such a disorder.

50. The method of claim 49, wherein the mammal is a human.

51. The method of claim 49, wherein the circulatory fluid is blood, plasma, serum or spinal fluid.

52. The method of claim 49 wherein the neurodegenerative disorder is Alzheimer's disease.

53. A method to determine if a mammal has a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, or a propensity to develop such a disorder, comprising:

(a) obtaining a circulatory fluid sample from the mammal; and

(b) determining a hydrogen peroxide level in circulatory fluid sample;

(c) determining the D-amino acid oxidase level in the circulatory fluid sample using the hydrogen peroxide level in step (b);

(d) comparing the D-amino acid oxidase level in the circulatory fluid from step (c) with a D-amino acid oxidase level in the circulatory fluid of a healthy control mammal(s), whereby an increased D-amino acid oxidase level in the circulatory fluid indicates the presence of or propensity to develop the degenerative or related disorder.

54. The method of claim 53, wherein the mammal is a human.

55. The assay of claim 53, wherein the circulatory fluid is blood, plasma, serum or spinal fluid.

56. The method of Claim 53 wherein the neurodegenerative disorder is Alzheimer's disease.

57. A method to determine if a mammal has a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, or a propensity to develop such a disorder, comprising measuring the

mammal's D-amino acid oxidase level and comparing the result to that obtained from a control mammal(s) with no degenerative or related disorder or a propensity to develop such a disorder.

58. The method of claim 53 wherein mammal's D-amino acid oxidase level is measured by determining a relative activity of the mammal's anti-oxidative enzymes compared to a control mammal(s) with no degenerative or related disorder or a propensity to develop such a disorder.

59. The method of claim 54 wherein the relative activity of the mammal's anti-oxidative enzymes is determined by quantitative PCR analysis of RNA that encodes the mammal's anti-oxidative enzymes compared to the control mammal(s), wherein a decreased level of RNA that encodes the mammal's anti-oxidative enzymes compared to the control mammal's level of the same RNA indicates the presence of the degenerative or related disorder or a propensity to develop the disorder.

60. The method of claim 59 wherein the mammal's RNA level is at least about 1.4-fold to about 3-fold higher than the control mammal's level of the same RNA.

61. The method of claim 59 wherein the anti-oxidative enzyme is glutathione S transferase, γ-glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase; glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase or NAD(P)H:quinone oxidoreductase.

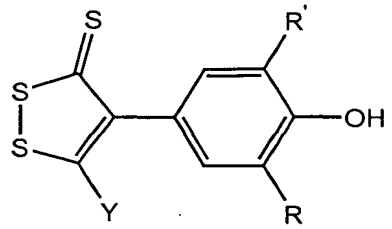
62. Use of one or more of the compounds of claim 1 or claim 11 for the manufacture of a medicament for a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a neurodegenerative-related disorder, or of treatment of malaria, a leishmania infection, or a trypanosome infection.

63. Use in a method of treatment of degenerative or related disorders, or of treatment of malaria or a trypanosome infection, said method comprising administering an effective amount of one or more to of the compounds of claim 1 or claim 11 a subject in need thereof.

64. Use of a D-amino acid oxidase inhibitor to treat or prevent a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder, a

neurodegenerative-related disorder, comprising administering to a mammal in need thereof an effective amount of the D-amino acid oxidase inhibitor.

65. A composition comprising a pharmaceutically acceptable carrier and a compound of the formula



wherein R and R' independently are the same or different and each is C1 - C12 alkyl or C5 - C12 cycloalkyl, either of which are optionally substituted with C1 - C4 alkyl or C7 - C14 aralkyl; and

Y is -H, -SH or $-SR^2$ where R^2 is C1 - C20 alkyl radical, C5 - C12 cycloalkyl, C3 - C20 alkenyl, or C7 - C14 aralkyl.

66. The composition of claim 65 wherein

(1) R and R^1 are branched-chain alkyl radicals having from 3 to 8 carbon atoms, 1-methyl cyclohexyl or $\alpha\alpha$-dimethyl benzyl;

(2) Y is an -S-alkyl group having from 6 to 18 carbon atoms; or

(3) the compound is 4-(3,5-di-isopropyl-4-hydroxyphenyl)-1,2-dithiole-3-thione, 4-((3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione, 4-[3,5-bis(1,1-dimethylpropyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 4-[3,5-bis(1,1-dimethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 4-[3,5-bis(1,1,3,3-tetramethylbutyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 4-[3,5-bis(1-methylcyclohexyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 4-[3,5-bis(1,1-dimethylbenzyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 4-(3-t-butyl-4-hydroxy-5-isopropylphenyl)-1,2-dithiole-3-thione, 4-(3-t-butyl-4-hydroxy-5-methylphenyl)-1,2-dithiole-3-thione, 4-[3-(1,1-dimethylpropyl)-4-hydroxy-5-isopropylphenyl]-1,2-dithiole-3-thione, 4-[3-(1,1-dimethylbenzyl)-4-hydroxy-5-isopropylphenyl]-1,2-dithiole-3-thione, 5-benzylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione, 5-benzylthio-4-[3,5-bis(1,1-dimethylpropyl)-4-hydroxy-phenyl]-1,2-dithiole-3-thione, 5-hexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione, 5-hexylthio-4-[3,5-bis(1,1-dimethylbutyl)-4-hydroxy-phenyl]-1,2-dithiole-3-thione, 5-octadecylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-

1,2-dithiole-3-thione, 5-octadecylthio-4-[3,5-bis(1,1-dimethylbenzyl)-4-hydroxyphenyl]-1,2-dithiole-3-thione, 5-allylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione, 5-cyclohexylthio-4-(3,5-di-t-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione or 4-(3,5-di-sec-butyl-4-hydroxyphenyl)-1,2-dithiole-3-thione.

67. A method to determine if a mammal has a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder or a neurodegenerative-related disorder, the method comprising

(1) taking a sample of circulatory fluid sample from a subject mammal and from a control mammal;

(2) determining the glutathione reductase levels in each circulatory fluid sample; and

(3) comparing the glutathione reductase levels, whereby a lower glutathione reductase level in the subject mammal compared to the control mammal indicates the presence or probable presence of the neurodegenerative disorder or the neurodegenerative-related disorder.

68. The method of claim 67 wherein the mammal is a human and the neurodegenerative disorder is Alzheimer's disease or Down's syndrome.

69. A method to determine if a mammal has a degenerative disorder, a neurodegenerative disorder, a degenerative-related disorder or a neurodegenerative-related disorder, the method comprising

(1) obtaining a suitable sample from a subject mammal;

(2) quantitatively determining the protein level or the enzyme activity of one or more of the mammal's anti-oxidative enzymes; and

(3) comparing the anti-oxidative enzyme protein or enzyme activity level from step (2) with a suitable normal control mammal, whereby a lower anti-oxidative enzyme protein or enzyme activity level in the subject mammal compared to the control mammal indicates the presence or probable presence of the degenerative disorder, neurodegenerative disorder, degenerative-related disorder or neurodegenerative-related disorder or a propensity to develop such a disorder.

70. The method of claim 69 wherein the anti-oxidative enzyme protein level or the enzyme activity level is one selected from glutathione S transferase, γ-

glutamylcysteine synthetase, glutathione reductase, glutathione peroxidase, epoxide hydrase, AFB_1 aldehyde reductase, glucuronyl reductase; glucose-6-phosphate dehydrogenase, UDP-glucuronyl transferase and NAD(P)H:quinone oxidoreductase.

71. The method of claim 70 wherein the anti-oxidative enzyme protein level or the enzyme activity level is the glutathione S transferase level.